Case Report

A Case of Sclerosing Angiomatoid Nodular Transformation of the Spleen: Correlations Between Contrast-enhanced Ultrasonography and Histopathologic Findings

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ABSTRACT: Sclerosing angiomatoid nodular transformation (SANT) is a recently recognized benign vascular lesion of the spleen. Detection of SANT as an incidentaloma has increased due to improvements in imaging techniques. However, a definitive diagnosis of SANT on CT or MRI remains difficult. We report the use of contrast-enhanced ultrasonography with Sonazoid in a case of SANT in a 50-year-old woman, with gross and microscopic pathologic correlations. © 2013 The Authors Journal of Clinical Ultrasound Published by Wiley Periodicals, Inc. *J Clin Ultrasound* **42**:103–107, 2014; Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jcu.22062

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Sclerosing angiomatoid nodular transformation (SANT) is a benign angioma-like disease of the spleen that was recognized as a district pathological entity in 2004 by Martel et al.[1] SANT differs from angiomas, which are true neoplasms, by the heterogeneity of its vascular components. The etiology of SANT has not been clarified, but its detection as an incidentaloma has increased due to improvements in imaging techniques, and SANT should be considered in the differential diagnosis of mass-forming lesions of the spleen. However, although more than 90 cases of SANT have been reported in the English literature, its definitive diagnosis on CT and MRI remains difficult.[2,3] Two reports have suggested the usefulness of contrast-enhanced ultrasonography (CEUS) using Sonovue for the diagnosis of SANT,[4,5] but results of CEUS of SANT using Sonazoid as a contrast agent have not been reported. In this study, we compared findings on preoperative CEUS with Sonazoid with histopathological findings in a patient diagnosed with SANT at surgery.

CASE REPORT

A 50-year-old woman was referred to our hospital after a mass of 32 mm in diameter in the spleen was found by ultrasonography (US) during a health check-up US examination. She had been healthy throughout her life and had no medical history. No abnormality was noted on physical examination at her first visit. Blood chemistry tests showed a slight increase in inflammatory reactions with a C-reactive protein level of 0.3 mg/dl (0.0–0.2 mg/dl), but white blood cell count, erythrocyte sedimentation rate, and IgG levels were normal, at 4000/μl (4000–9000/μl), 7 mm/hr, and 1107 mg/dl (703–1540 mg/dl), respectively. Viral markers, antinuclear

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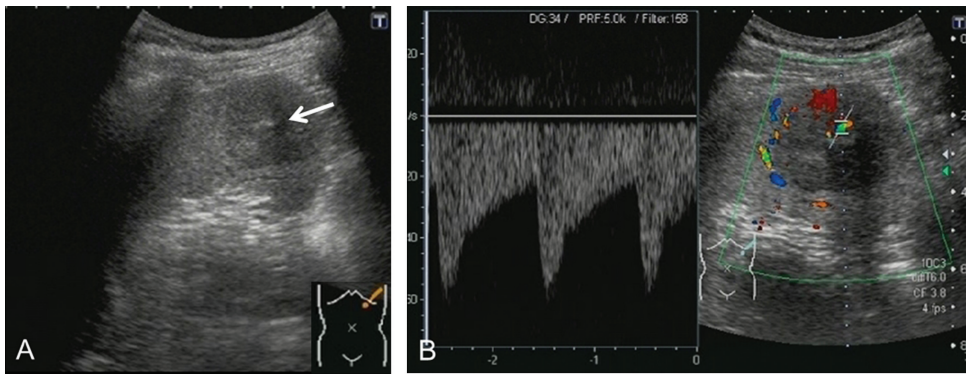

FIGURE 1. Gray-scale and Doppler ultrasound examination. **(A)** A left intercostal gray-scale ultrasonography shows a 32 × 27 mm hypoechoic mass in the lower pole of the spleen with bright linear echoes accompanied by acoustic shadow in the center (arrow). **(B)** Spectral Doppler analysis shows arterial signals in the center of the mass.

antibody level, were normal. Tumor markers were also within normal limits with CEA of 0.5 ng/ml (normal range, 0.0–5.0 ng/ml), and CA125 of 9.2 U/ml (0.0–35.0 U/ml). sIL-2R level was 301 U/ml (220–530 U/ml) and the von Willebrand factor antigen level was 73% (50–155%).

On unenhanced CT, a heterogeneous low-density mass of 31 × 28 mm with a blurred border was noted at the lower pole of the spleen. On dynamic CT, the border between the mass and splenic parenchyma was clearly delineated. The mass was gradually enhanced from the arterial to the portal phase in a periphery-predominant manner, and the entire mass, except the central low-density area, appeared isodense to the splenic parenchyma in the equilibrium phase. The splenic mass showed isointensity on T1-weighted MRI, a starfish-like low intensity in the center on fat-suppressed T2-weighted imaging, and isointensity in the periphery.

Gray-scale US through a left intercostal approach showed a 32 × 27 mm hypoechoic mass in the lower pole of the spleen. Bright linear echoes accompanied by acoustic shadowing were seen in the center (Figure 1A), which showed blood flow signals on color Doppler imaging and an arterial waveform on spectral Doppler analysis (Fig. 1B).

CEUS was performed using an SSA-790A system (Toshiba Medical Systems, Tokyo, Japan) with a convex probe (PVT-375BT, 3.75-MHz center frequency). Sonazoid (Daiichi-Sankyo, Tokyo, Japan) was injected as a bolus through the median cubital vein at 0.5 ml/body followed by a 10-ml normal saline flush, and the mass was observed by placing the focus at the lower margin of the mass and setting the mechanical index level to 0.2. In the early vascular phase, a spoke-wheel-like enhancement extending radially from the center of the mass appeared at 12 seconds after administration of the contrast agent, and almost complete enhancement, which was weaker than the contrast enhancement in the splenic parenchyma, was observed after 23 seconds (Figure 2A–2C). Fifteen minutes after contrast administration in the postvascular phase (so-called Kupffer phase), enhancement persisted in the periphery of the mass (Figure 2D). To examine the distribution of Sonazoid bubbles accumulated in splenic reticuloendothelial cells, the center of the mass was insonated at high acoustic pressure (flash method),[6] confirming the pooling of the contrast agent in the periphery of the mass (Figure 2E).

Overall evaluation of the imaging findings suggested that the splenic mass was a solid heterogeneous mass with different tissues in the center and at the periphery. On dynamic CT, the mass appeared hypovascular, but the CEUS findings of vascularization extending radially from the center suggested that the tumor had a relatively rich blood supply. Also, as the contrast agent remained primarily in the periphery of the mass in the postvascular phase of CEUS, the presence of reticuloendothelial cells or blood sinuses resembling hemangioma was suspected. On the basis of the clinical course, blood chemistry test results, and imaging findings, a benign disease such as splenic inflammatory pseudotumor, hemangioma, or littoral angioma was suspected, rather than a malignant tumor. However, laparoscopic splenectomy was performed at the patient's request.

In cross-sections of the resected specimen, a 34 × 33 × 24 mm mass was noted at the lower pole of the spleen. White stellate extensions of fibrosis were present in the center of the mass and many reddish-brown angiomatoid nodules

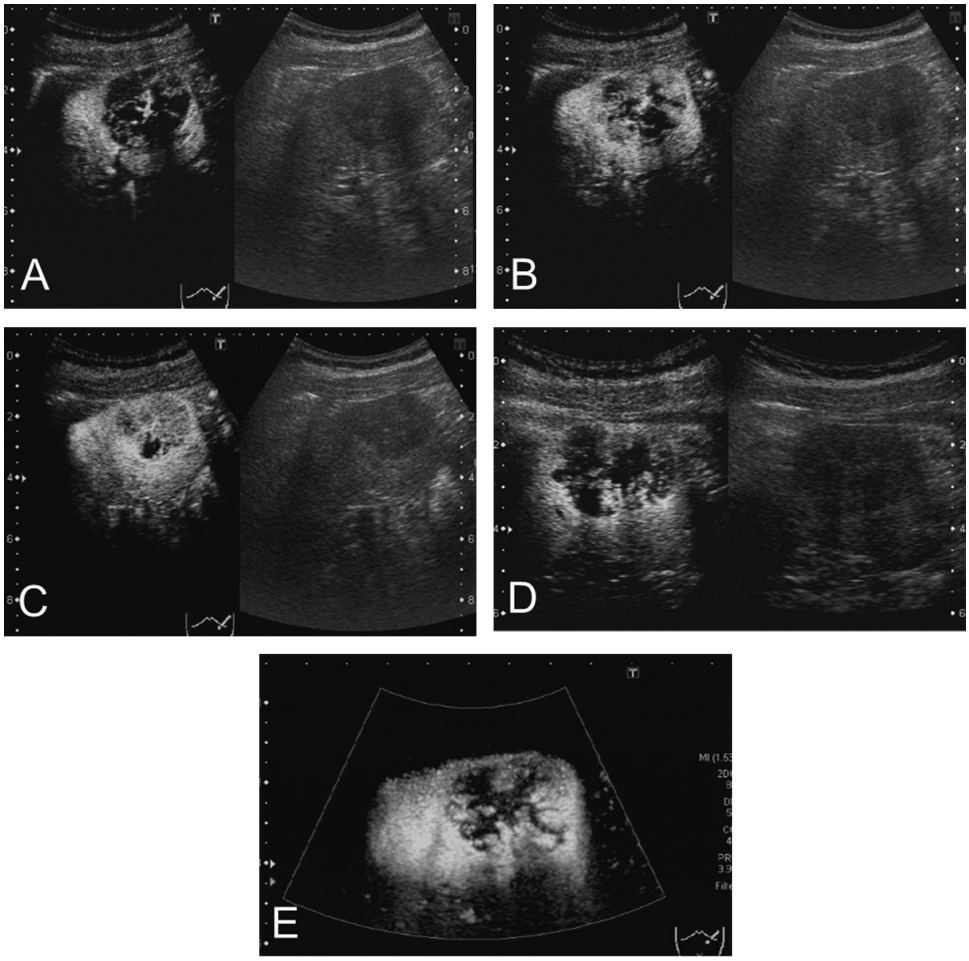

FIGURE 2. Contrast-enhanced ultrasound examination. **(A)** In the early vascular phase, a spoke-wheel-like enhancement extending radially from the center of the mass appeared at 12 seconds after administration of the contrast agent. **(B)** A densely enhanced portion then spread through the tumor. **(C)** Almost the whole tumor was enhanced after 23 seconds **(D)**. In the postvascular phase, 15 minutes after injection, there is residual pooling of contrast agent in the periphery of the mass **(E)**. The contrast-enhanced image is obtained after high acoustic pressure; insonation confirms the pooling of the contrast agent at the periphery of the mass.

of irregular size were observed in the periphery (Figure 3A). Histopathological examination showed no clear capsule formation in the tumor, but the border with normal splenic tissue was clear. In the tumor, nodular capillary growths separated by fibrous tissue were observed with proliferation of spindle cells accompanied by mild chronic inflammatory cell infiltration in the background (Figure 3B and 3C). Hemosiderin-laden macrophages and extravasated red blood cells were present within the nodules. Endothelial cells in these nodules showed a heterogenous immunohistological profile of CD31(+)/CD34(+)/CD8(−) cells, which are characteristic of cord capillaries; CD31(+)/CD34(−)/CD8(−) cells in small veins; and CD31(+)/CD34(−)/CD8(+) cells in sinusoid spaces. These findings and the characteristic macroscopic features led to the diagnosis of SANT. The $IgG4^+/IgG^+$ plasma cell ratio (IgG4/IgG ratio) in the tumor was increased to 35%.

DISCUSSION

SANT was first reported in 2004 by Martel et al[1] in a report of 25 cases of benign mass-forming vascular lesions of the spleen exhibiting characteristic morphologic features. The disease has not been widely recognized because the concept was proposed only recently. However, the same condition used to be referred to as cord capillary hemangioma, benign vascular neoplasm of the spleen with myoid and endotheliomatous features, or multinodular hemangioma, and thus its incidence is likely to be relatively high.[7,8] The mass is often

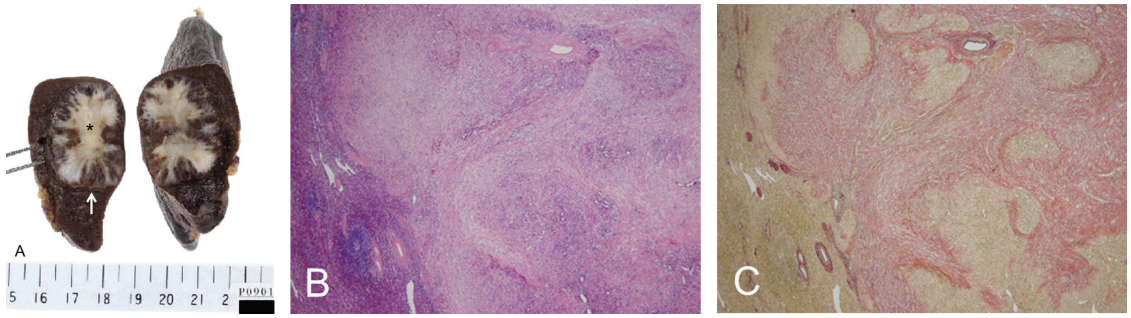

FIGURE 3. Gross pathologic and histopathological findings. **(A)** Cut specimen shows a scar-like white fibrous center (*) with spoke-wheel radiating white fibrous strands and angiomatoid nodules (arrow) in the periphery. **(B, C)** Low-power photomicrographs show multiple small and large sclerosing nodules separated by stromal fibrosis with associated inflammatory cells (**B**: hematoxylin and eosin, ×4; **C**: Elastica van Gieson, ×4).

asymptomatic, as in our patient, affects women more frequently, and is often detected incidentally during imaging tests.[1] SANT involves the formation of multiple angiomatoid nodules and an inflammatory fibrotic interstitium reminiscent of inflammatory pseudotumor. The composition of the nodules is heterogeneous and is characterized by three different vascular components: CD31(+)/CD34(+)/CD8(−) cord capillaries, CD31(+)/CD34(−)/CD8(−) small veins, and CD31(+)/CD34(−)/CD8(+) sinusoid spaces. In contrast, true angiomas, such as splenic hemangioma and littoral angioma, consist of homogeneous vascular components.[9]

The etiology of SANT is unclear, and it has been suggested that SANT would be related to a systemic inflammatory reaction and Epstein–Barr virus infection, arise from inflammatory pseudotumor, or be an organized hematoma secondary to circulation disorder or trauma.[1,10,11] In our patient, the IgG4/IgG ratio was high, at 35%, and several recent reports also suggested a relationship of SANT with IgG4-related diseases.[12] However, the problem remains unsolved and further accumulation of cases will be necessary to elucidate the etiology of SANT.

SANT's gross characteristics include a whitish, thick, fibrous interstitium radiating from the center in a stellate pattern and multiple angioma-like, reddish-brown nodules in the periphery surrounded by a fibrous interstitium. This heterogeneity is reflected by the imaging findings. Typically, on CT, SANT appears as a low-density tumor, which exhibits persistent delayed peripheral enhancement after slow contrast enhancement, similar to hepatic hemangiomas. This reflects the hemangioma-like components in the periphery.

CEUS has better temporal resolution than contrast-enhanced CT and is capable of displaying blood flow in the mass in real-time. Moreover, CEUS using Sonazoid, unlike Sonovue, can both dynamically visualize blood flow distribution in the tumor in the vascular phase and detect tumors in the postvascular phase, because Sonazoid is taken up by reticuloendothelial cells of the spleen, similar to the Kupffer cells in the liver.[13,14] In our patient, the CEUS findings of spoke-wheel-like enhancement from the center in the early vascular phase correlated with histopathological findings of whitish, thick star-like fibrous interstitium containing the proliferating vessels. In the postvascular Kupffer phase, Sonazoid was taken up by the periphery of the mass beyond 15 minutes after injection, which reflects the presence of reticuloendothelial cells (eg, macrophages) and sinusoids in the areas of the spleen showing hemangioma-like, reddish-brown nodules.

The results of CEUS using Sonovue have been described in one case by Gutzeit et al[4] and 2 cases by Cao et al.[5] The spoke-wheel-like enhancement observed in our patient in the early vascular phase was also reported by Gutzeit et al and in one of the cases of Cao et al. These findings resemble focal nodular hyperplasia in the liver and are thought to be characteristic of SANT in the spleen. Retention of contrast agent in the periphery of the tumor was observed after 4 or more minutes by Gutzeit et al[4] and after 3 and 7 minutes in the two cases described by Cao et al,[5] without discussion of the cause. The uptake of Sonazoid contrast agent in the postvascular phase, as observed in our patient, may be useful for exclusion of malignant tumors such as lymphoma and metastatic tumors, which often appear as hypoechoic nodules in the spleen.

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